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## Renal replacement therapy in patients with familial Mediterranean fever

Bahman Bashardoust\*, Bahram Bashardoust, Maryam Ghavami, Nasrin Shami

Department of Internal Medicine, Ardabil University of Medical Sciences, Ardabil, Iran

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### ABSTRACT

One of the causes of end-stage renal disease (ESRD) in some countries is the renal involvement caused by the complications of the familial Mediterranean fever (FMF). Amyloidosis is of the most important complications of FMF that can lead to ESRD. We report our experiences of FMF patients with ESRD who received hemodialysis and kidney transplantation over the past 17 years. Of nine patients, four had amyloidosis, two had focal segmental glomerulosclerosis (FSGS), one had IgA nephropathy, and two did not undergo biopsy because their kidneys were atrophic. Of the nine patients, one died of amyloidosis. Seven patients had kidney transplantation and one patient is currently undergoing dialysis. Six patients were transplanted from a living donor and one from a cadaver. The ultrasound examination revealed that five patients had bilateral kidney atrophy, four patients had normal size kidney with amyloidosis. None of the seven patients who underwent renal transplantation had a history of rejection. Kidney transplantation and hemodialysis in patients with FMF is similar to those with other ESRD etiologies.

### *Implication for health policy/practice/research/medical education:*

Kidney transplantation and hemodialysis in patients with FMF is similar to those with other ESRD etiologies. In fact kidney transplantation is more preferable for ESRD due to FMF, as in other patients. They appear to have no higher mortality than other patients, and colchicine should be continued after transplantation.

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### Introduction

Familial Mediterranean fever (FMF) is an autosomal recessive disease characterized by recurrent episodes of abdominal, chest and joint pain (polyserositis). These episodes are often accompanied by fever and sometimes skin rashes (1). About 90% of episodes occur before the age of 20 (2). FMF is seen in certain ethnic groups such as Jews, Armenians, and Turks (3). In Iran, FMF is observed in the Azarbaijan region. One of the long-term complications of FMF is secondary amyloidosis. Renal involvement starts with proteinuria and eventually leads to nephrotic syndrome. After renal involvement, end-stage renal disease (ESRD) occurs within 2-13 years on average (2). Secondary amyloidosis has been reported as the most common cause of death in FMF (4). Before treatment of FMF with colchicine, amyloidosis was reported in 30%

of Jews and 60% of Turks (5). Amyloidosis is rarely seen in Jews living in the United States (6). Other renal diseases have been reported in FMF, such as Henoch–Schönlein purpura, polyarteritis nodosa, glomerulonephritis, and focal segmental glomerulosclerosis (FSGS) (7).

ESRD can be managed with dialysis or kidney transplantation in patients who develop it, as in other patients (8). In patients with FMF, gastric emptying is delayed and sometimes there are more drug-related complications, such as neuropathy (9,10).

### Patients and Methods

We monitored the patients from 2006 to 2018 and hereby share our experiences. FMF is diagnosed based on Tel-Hashomer criteria and detecting FMF gene and a dramatic response to colchicine. Like other ESRD

\*Corresponding author: Bahman Bashardoust,  
Email: b\_bashardoust@yahoo.com

patients, hemodialysis and kidney transplantation are considered in these patients. This study followed the tenets of the Declaration of Helsinki.

## Results

Of nine patients, six were male and three were female. Kidney involvement (ESRD) was higher in males (66.6%) than that in females. Of the nine patients, four were diagnosed with amyloidosis, two with FSGS and two did not undergo biopsy. Of the nine patients, five had atrophic kidneys (55.5%). Four patients with normal-size kidney were diagnosed to have amyloidosis. Of nine patients, seven were received kidney transplantation, and two patients with ESRD underwent hemodialysis. One patient died after two years of dialysis (a 27-year-old female) due to infection and heart failure. She had amyloidosis. No heart problems were observed in other patients.

Mean age of patients was 37 years. The youngest patient was a 24-year-old male and the oldest was a 52-year-old male. Mean kidney transplantation duration was 6.4 years. Mean dialysis duration in patients was 2.3 years. Mean creatinine in patients was 1.1 mg/dL. The minimum amount was 0.8 mg/dl with four years of transplantation and the maximum value was 1.3 mg/dl with 11 years of transplantation. None of our patients had a rejection episode. One case was resistant to treatment which was controlled by 2 mg of colchicine per day. One of our patients refused to take oral colchicine, and had 800 mg daily proteinuria in 24-hour urine with six years of transplantation, which decreased to 215 mg in 24-hour urine after 6 months of taking colchicine. All patients were treated with colchicine. Of the seven patients, one received transplantation from a cadaver and the rest from living unrelated. Of the seven patients, four were treated with mycophenolate mofetil and cyclosporine, two with tacrolimus and mycophenolate mofetil, and one with tacrolimus and azathioprine. All patients received prednisolone. Three of the seven patients had

hypertension. None of the patients had diabetes and did not develop diabetes after transplant. One patient was treated with allopurinol for treatment of hyperuricemia and three patients were treated for hyperlipidemia. Hemodialysis patients had no episodes and did not require colchicine. A hemodialysis patient diagnosed with primary amyloidosis was treated with chemotherapy, who had a positive Mediterranean fever gene and family history; therefore, the chemotherapy discontinued and the patient was referred for transplantation (Table 1).

## Discussion

Kidney transplantation is a specific treatment for most ESRD patients. However, specific backgrounds in ESRD can cause many problems for kidney transplantation. Several systems are involved if patients with FMF develop amyloidosis.

Kidney transplantation is also preferred in amyloidosis. The exception is a heart involvement that can be a contraindication to transplantation, especially if patients' life expectancy is less than three years. FSGS was one of the causes of ESRD in FMF in this study.

The outcome of comorbidity of amyloidosis and cardiac involvement is poor (11). Life expectancy is expected to be less than three years with cardiac involvement along with FMF-induced amyloidosis (12).

Preparing patients with FMF for kidney transplantation is just like any other patient. However, these patients need to start taking colchicine after the surgery (13). If these patients do not pay attention to the FMF episodes, they may be misdiagnosed as acute abdomen and after transplantation, the patient may need to undergo diagnostic laparotomy. FMF is unknown to many transplantation centers and can relapse immediately after transplantation, which happened to one of our patients. This patient was repeatedly examined for fever episodes. In these patients, fever episodes that have no reason can be due to FMF (14). However, other causes must be considered, too (15).

**Table 1.** Data of patients

Gender	Age	RRT	Treat	Creatinine	Colchicine	Rejection	HTN	Gene	Pathology	Familial
Male	52	Transplant	PMC	1.3 mg/dL	1 mg	N	Y	V726A/A744S	-	Y
Male	48	Transplant	PMC	1.2 mg/dL	1 mg	N	y	-	FSGS	Y
Male	38	Transplant	PMT	1.1 mg/dL	1 mg	N	N	-	IgA nephropathy	N
Male	36	Transplant	PMC	1.1 mg/dL	1 mg	N	y	-	-	N
Male	39	Transplant	PMT	1.3 mg/dL	2 mg	N	Y	-	Amyloidosis	Y
Female	34	Transplant	PAT	0.8 mg/dL	2 mg	N	N	V726A/M694V	FSGS	Y
Female	35	Hemodialysis	-	-	-	-	N	M694V/M694v	Amyloidosis	Y
Female	27	Hemodialysis	-	-	-	-	N	-	Amyloidosis	N
Male	24	Transplant	PMC	1.2	1 mg	N	N	-	Amyloidosis	Y

We discontinued colchicine in an asymptomatic patient who did not consent to take the medication. He developed proteinuria after 6 years (800 mg in 24-hour urine). It appears that colchicine should continue even in asymptomatic patients. After starting colchicine, the protein decreased to 217 mg in 24-hour urine. After transplantation, FMF episodes are more likely to occur and immunosuppressive medications are not effective in preventing them, whereas these episodes are fewer and with minor and transient symptoms in ESRD. Erythrocytosis was observed in two of our patients, which was controlled with enalapril. The causes of erythrocytosis after transplantation are renal cysts, renal artery stenosis, hydronephrosis, pulmonary disease, and renal tumors (16). In some studies, FMF-associated amyloidosis is thought to be the cause of erythrocytosis.

None of our patients experienced rejection. The mean serum creatinine of our patients was 1.3 mg/dL and the lifetime of the transplanted kidney and patient survival was 100% in the first, fifth and tenth years. One patient changed to azathioprine because she planned to get pregnant, but she did not become pregnant after 5 years. In these patients, there is a possibility of early ovarian failure. In some studies, treatment with cyclosporine was reported to produce poor outcomes (17). Meanwhile, there was no particular problem with this treatment in our patients. Celik et al observed early mortality with high infectious complications, however none of our patients had serious infections causing hospitalization; since, the number of our patients was low, though (18).

### Conclusion

Kidney transplantation is more preferable for ESRD due to FMF, as in other patients. They appear to have no higher mortality than other patients, and colchicine should be continued after transplantation. Since our sample size was low, it is recommended to conduct multicenter studies.

### Limitations of the study

The disease has been studied in a small number of patients, while the disease is less common and has fewer side effects.

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### Authors' contribution

In this study Bahman Bashardoust was the corresponding author. Bahram Bashardoust performed data collection. Maryam Ghavami analyzed the results and interpreted data. Bahman Bashardoust prepared the manuscript. All authors have read and approved the content of manuscript.

### Conflicts of interest

The authors have no conflicts of interest to disclose.

### Ethical issues

The research followed the tenets of the Declaration of Helsinki. The informed consent was obtained from all the participants. Moreover, ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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